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**Project Title:** Biology and biochemistry of Jelly belly signaling

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**Abstract:** *DESCRIPTION (provided by applicant): The objective of the proposed experiments is to understand the role of a newly discovered signaling system that controls Drosophila smooth muscle development in human cardiovascular development and disease. The secreted signaling protein Jelly belly regulates embryonic smooth/visceral muscle migration and differentiation in Drosophila. Jeb acts through the receptor tyrosine kinase, DAlk, a high-affinity, tissue specific receptor. DAlk is the Drosophila homologue of a human proto-oncogene, Anaplastic Lymphoma Kinase (ALK). The identification of DAlk as the Jeb receptor establishes that this signaling system is conserved in mammals. The proposed experiments extend recent work in Drosophila on the developmental function of this signaling system to mammalian development and disease. In Drosophila Jeb regulates org-1, a homologue of human TBX1. TBX1, a T-box transcription factor, is required for normal cardiovascular development in mice and is the gene responsible for congenital cardiovascular malformations associated DiGeorge/Velo-cardio-facial Syndrome. Besides org-1, Jeb also regulates the "muscle fusion pathway" in embryonic visceral muscle, this hierarchical system of muscle patterning, well characterized in Drosophila, has conserved components in mammals. The proposed experiments test the hypothesis that the developmental functions of Jeb signaling through DAlk are conserved, and that Jeb homologues regulate cardiovascular development, TBX1 and the muscle fusion pathway in mammals. Like most receptor tyrosine kinases, DAlk is activated by dimerization. Jeb, the ligand for DAlk, is synthesized and secreted as a monomer. The mechanism of ligand dependent dimerization and activation of DAlk is therefore not readily apparent. Two, distinct mechanisms have been defined for ligand dependent activation of the FGF and EGF receptor tyrosine kinases respectively. To clarify the mechanisms of ligand dependent activation of DAlk, systematic mutagenesis experiments will map domains required for ligand binding and receptor activation. The extracellular matrix associated proteins Pleiotrophin (Ptn) and Midkine (Mk) have been reported to bind and activate ALK. They also have proposed roles in angiogenesis, oncogenesis, wound repair and learning. To define the roles of Ptn and Mk, mutants of a Drosophila Ptn/Mk homologue will be generated and its phenotypes analyzed. Analysis of the phenotype of Ptn/Mk mutants in Drosophila will clarify the signaling function of these molecules both with respect to the pathways in which they participate and their functions in those pathways.*